

Mechanisms of Conjugated Linoleic Acid in Health and Disease

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Outline

- Immune and anti-inflammatory effects
- Factors maximizing the immunological impact
- Controversy
- Potential Mechanisms
- Gaps in CLA research

CLA in Immune and Inflammatory Dysfunction

- Anti-inflammatory
 - TNF- α and nitric oxide are suppressed
 - IL-1 and IL-6 expression
- Enhances adaptive immune responses
 - IL-2 production
 - Numbers and effector functions of CD8⁺ cells

Amelioration of Colonic Inflammation by CLA



H & E stained sections of porcine colonic tissue, $\times 63$.

Immunological Mechanisms

- Modulation of cytokine expression
 - Down-modulation of T helper 2 cytokines
 - IL-10 and IL-4
 - Down-modulation of T helper 1 cytokines
 - IFN- γ and IL-12
 - Possible inhibition of helper T cell polarization
- Proliferative responses of T cells

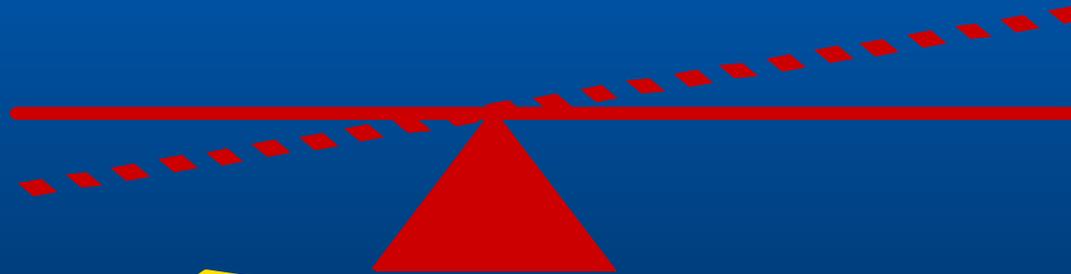
Modulation of the T helper cell polarization

T helper 1 cytokines

IFN- γ
IL-12

T helper 2 cytokines

IL-4
IL-5
IL-10

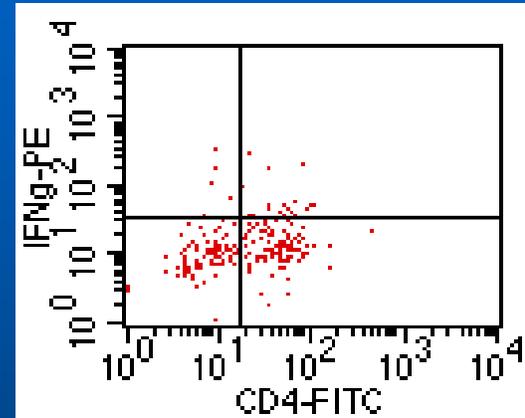
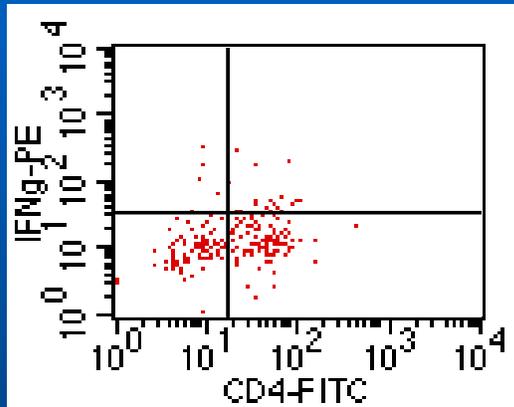


Dendritic Cells

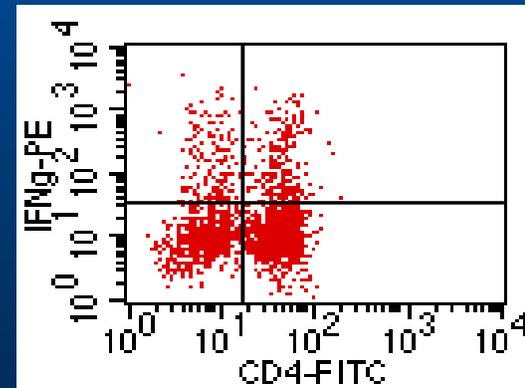
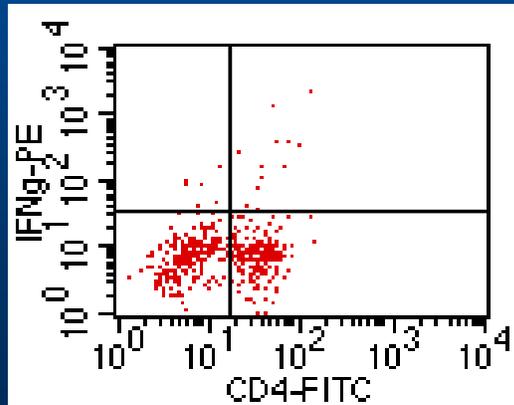
Antigen-specific IFN- γ

Non-stimulated

ORF2-stimulated

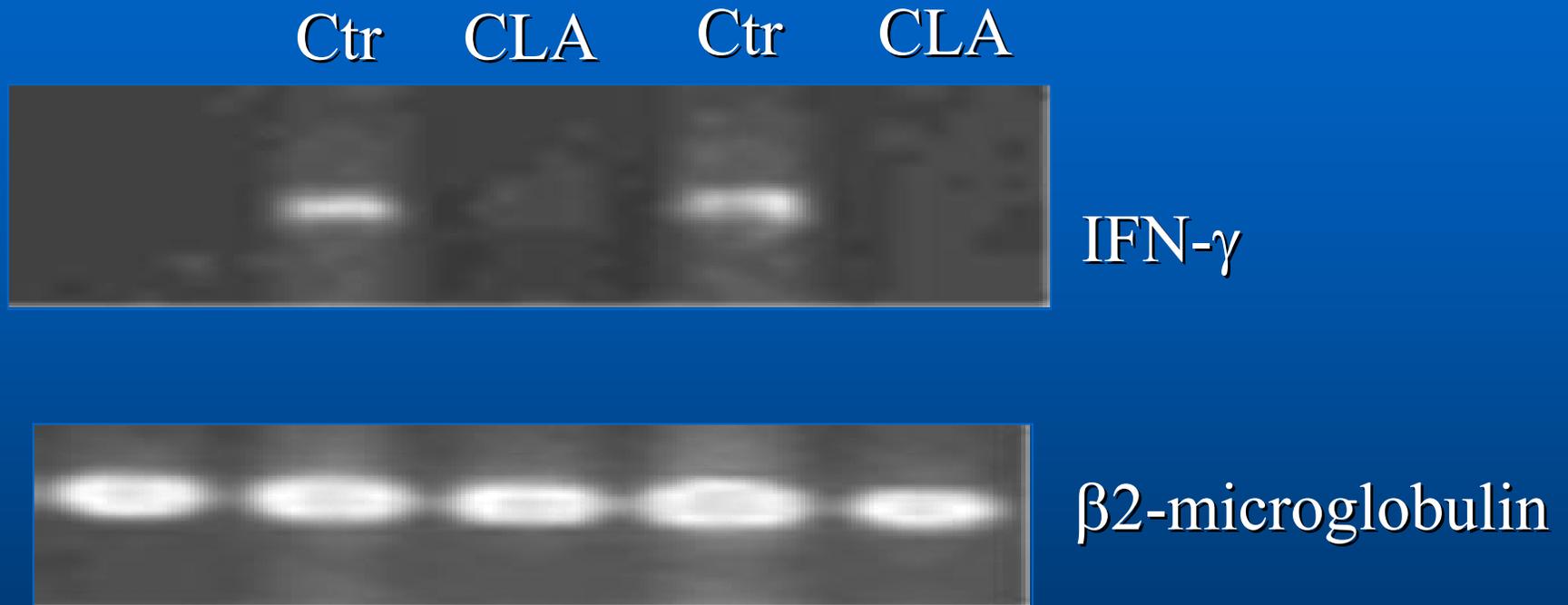


CLA



Control

IFN- γ mRNA Expression

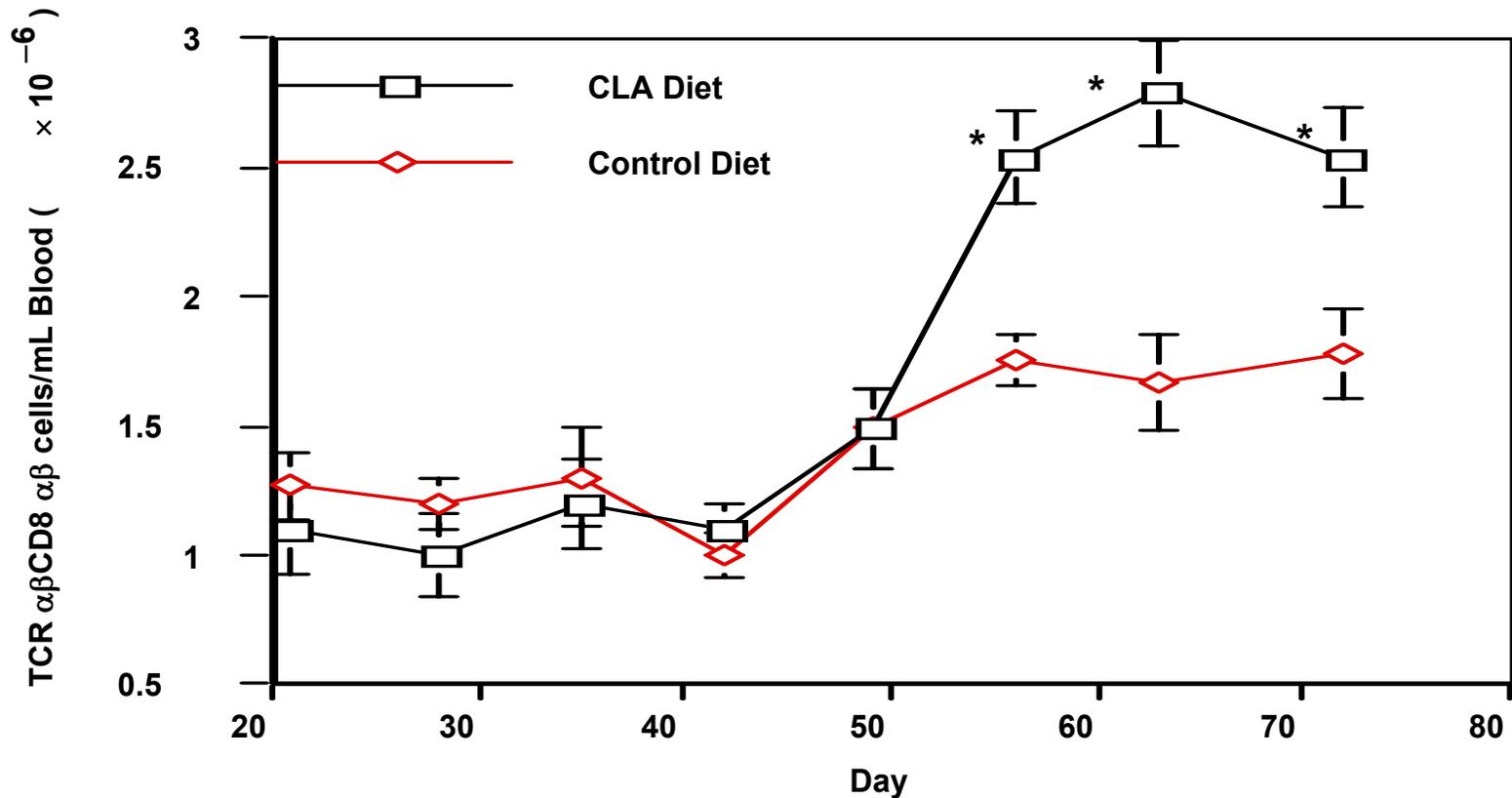


RT-PCR using RNA recovered from colonic lymph nodes

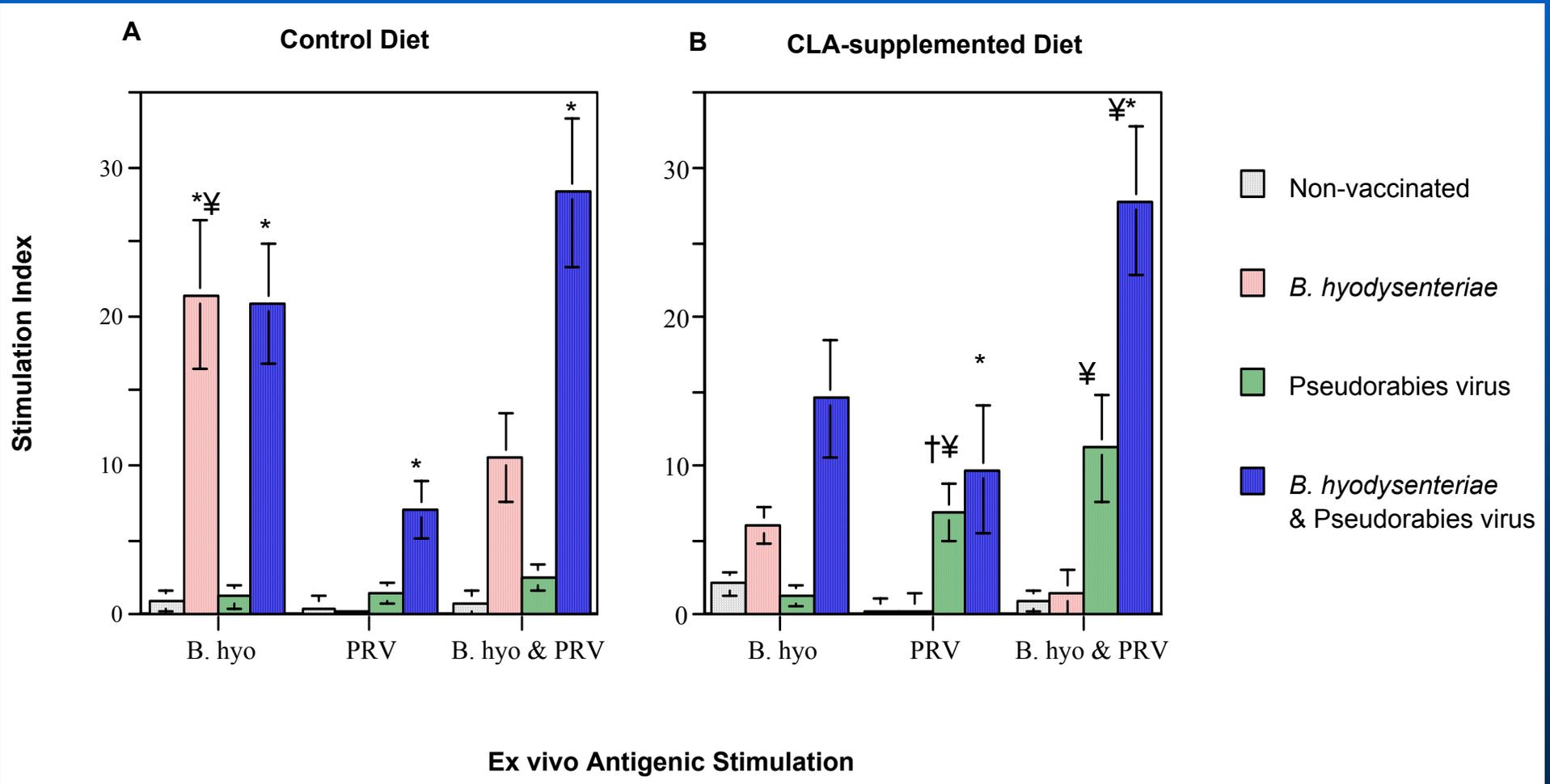
Immunological Benefits

- CLA fed early in life
 - Development of the immune system
- Requirement for a period of accumulation
 - Thymus size and composition at d 28
 - Numbers of peripheral lymphocytes at d 42
- Optimized in disease states
 - Autoimmune
 - Inflammatory

Dietary Regulation of Numbers of CD8⁺ lymphocytes



Antigen-specific Proliferation of PBMC



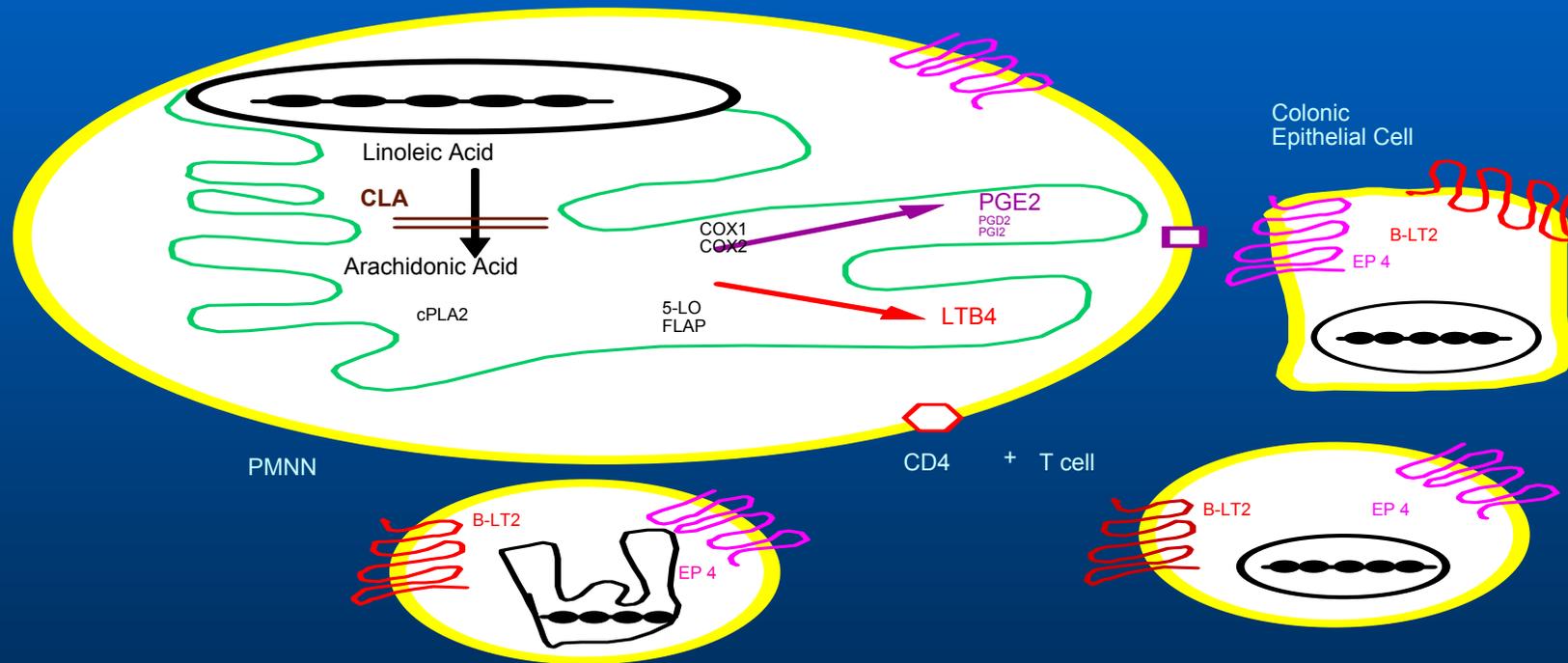
Controversy

- Enhanced immune function
 - Animal models (mice, rats, and pigs)
 - In vitro (lymphocyte cultures)
- No effects
 - Human trial (Kelley et al., 2000)
 - CLA does not affect the immune status
 - Poor CLA source

Potential Explanations for the Immunological Effects of CLA

- Endoplasmic Pathway
 - Decreased eicosanoid synthesis
- Nuclear Pathway
 - Enhanced expression and activation of PPAR- γ

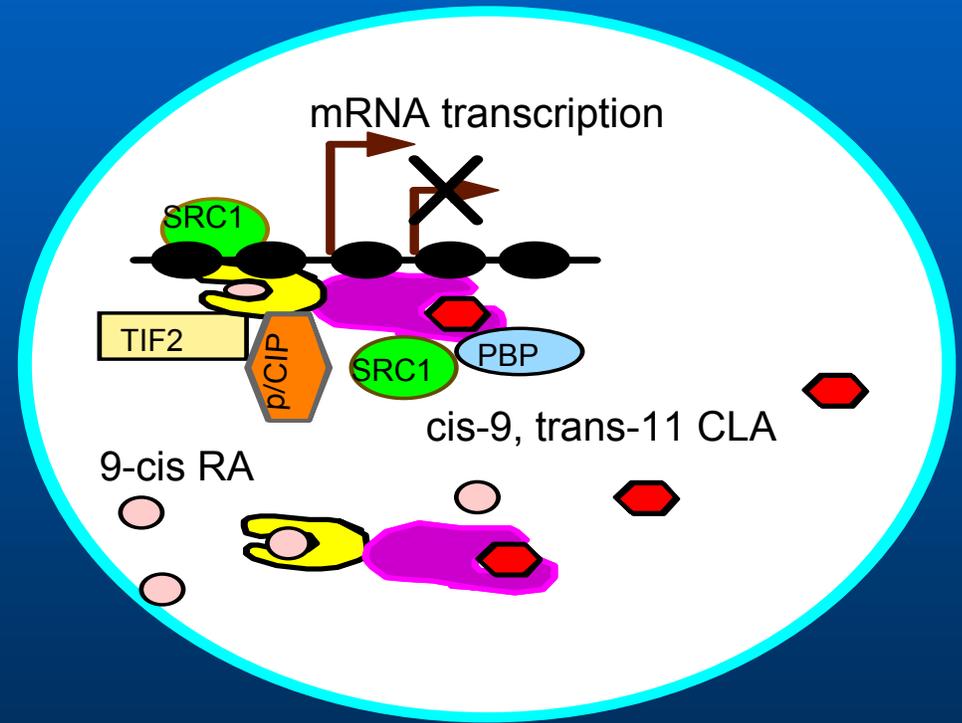
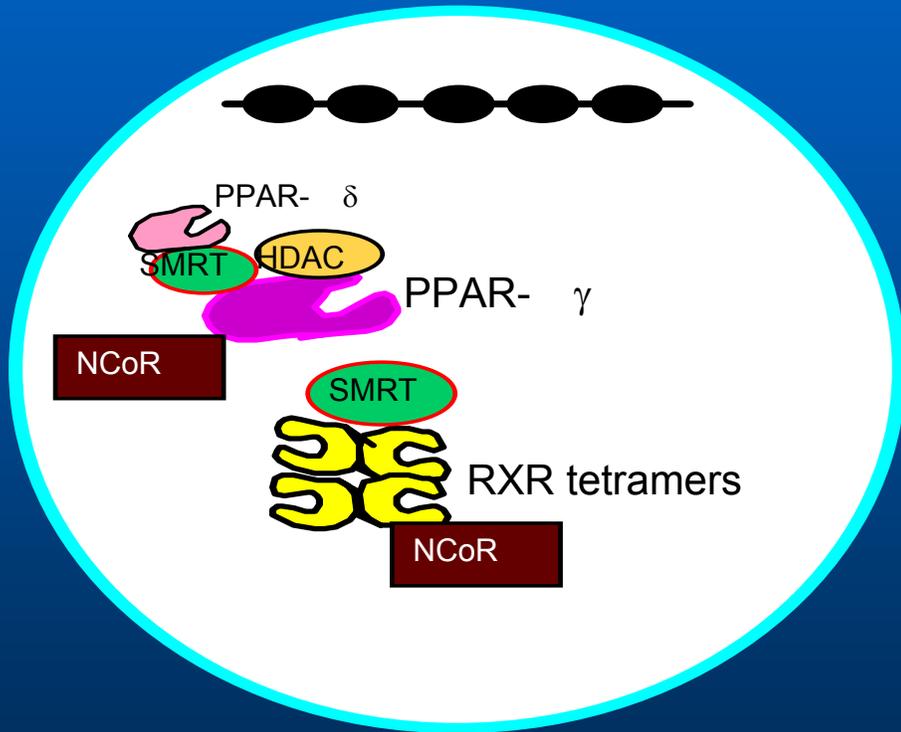
Endoplasmic Pathway



Endoplasmic Pathway

- CLA decreases eicosanoid production
- Eicosanoids
 - Modulate cytokine production
 - Involved in inflammation
 - Involved in cancer

Nuclear Pathway



Nuclear Pathway

- CLA enhances PPAR- γ expression in vivo
- CLA enhances PPAR- γ activation in vitro
- Both known PPAR- γ agonists and CLA
 - Prevent mucosal inflammation
 - Similar modulation of cytokine production
 - Are anti-diabetic
 - Are anti-carcinogenic

Gaps in CLA research

- Poor mechanistic understanding in physiologically relevant models
 - Nuclear pathway
 - Endoplasmic pathway
 - Synergies and/or antagonisms
- Limited number of studies using specific isomers
- Limited number of human studies